

Novel Formulation

This application claims the benefit of priority from Provisional Application
5 No. 60/239,781 filed 12 October 2000.

This invention relates to a novel formulation comprising using amoxicillin and potassium clavulanate and the use thereof in treating bacterial infections.

Amoxicillin and potassium clavulanate are respectively a known β -lactam antibiotic and a known β -lactamase inhibitor. Products comprising amoxicillin and potassium clavulanate are marketed under the trade name "Augmentin" by SmithKline Beecham. Such products are particularly effective for treatment of community acquired infections, in particular upper respiratory tract infections in adults and otitis media in children.

Various tablet formulations of amoxicillin and potassium clavulanate have been approved for marketing, comprising various different weights and ratios of amoxicillin and potassium clavulanate, for instance, conventional swallow tablets comprising 250/125, 500/125, 500/62.5, and 875/125 mg amoxicillin/clavulanic acid (in the form of potassium clavulanate). Such tablets comprise amoxicillin and clavulanic acid in the ratio 2:1, 4:1, 8:1 and 7:1, respectively. The 875/125 mg tablet was developed to provide a tablet formulation which could be administered in a bid (twice daily) dosage regimen. It is also marketed for tid (three times daily) dosing, in Italy and Spain. The 500/62.5 mg tablet was also developed to provide a tablet formulation which could be administered in a bid dosage regimen, two such tablets being taken every 12h, in preference to a single 1000/125 mg tablet. A 25 1000/125mg single dosage is also available, in France, but as a single dosage sachet rather than a tablet. Typically, the approved regimens provides a single dosage of 125 mg of potassium clavulanate. In addition, WO 97/09042 (SmithKline Beecham) describes tablet formulations comprising amoxicillin and clavulanic acid in a ratio in the range 12:1 to 20:1, preferably 14:1.

WO 94/16696 (SmithKline Beecham) discloses generally that clavulanic acid may unexpectedly enhance the efficacy of amoxicillin against microorganisms having a resistant mechanism which is not β -lactamase mediated.

Existing marketed tablet formulations of amoxicillin and potassium clavulanate are conventional in that they provide immediate release of the active ingredients once the tablet reaches the stomach. There has also been some interest in developing formulations in which the release profile is modified, to allow for a

longer interval between dosages, for instances, every 12 hours (bid, q12h), rather than every 8 hours (tid, q8h).

Thus, for instance, WO 95/20946 (SmithKline Beecham) describes layered tablets comprising amoxicillin and, optionally, potassium clavulanate, having a first layer which is an immediate release layer and a second layer which is a slow release layer. The broadest ratio of amoxicillin to clavulanic acid is 30:1 to 1:1, with a preferred range of 8:1 to 1:1. Amoxicillin is suitably in the form of amoxicillin trihydrate. Examples provided in WO 95/20946 of such bilayered tablets have amoxicillin trihydrate in the immediate release layer and amoxicillin plus clavulanate in the slow release layer. Multi-layered tablets are described more generically in WO 94/06416 (Jagotec AG). Further bilayered tablets comprising clavulanic acid and amoxicillin are described in WO 98/05305 (Quadrant Holdings Ltd). In such tablets, a first layer comprises amoxicillin and a second layer comprises clavulanate and the excipient trehalose, to stabilise the clavulanate component.

In addition, WO 95/28148 (SmithKline Beecham) describes amoxicillin / potassium clavulanate tablet formulations having a core containing amoxicillin and potassium clavulanate coated with a release retarding agent and surrounded by an outer casing layer of amoxicillin and potassium clavulanate. The release retarding agent is an enteric coating, so that there is an immediate release of the contents of the outer core, followed by a second phase from the core which is delayed until the core reaches the intestine. Furthermore, WO 96/04908 (SmithKline Beecham) describes amoxicillin/potassium clavulanate tablet formulations which comprise amoxicillin and potassium clavulanate in a matrix, for immediate release, and granules in a delayed release form comprising amoxicillin and potassium clavulanate. Such granules are coated with an enteric coating, so release is delayed until the granules reach the intestine. WO 96/04908 (SmithKline Beecham) describes amoxicillin/potassium clavulanate delayed or sustained release formulations formed from granules which have a core comprising amoxicillin and potassium clavulanate, surrounded by a layer comprising amoxicillin. WO 94/27557 (SmithKline Beecham) describes controlled release formulations of amoxicillin and clavulanic acid prepared using a hydrophobic waxy material which is then subjected to thermal infusion.

Controlled release formulations comprising amoxicillin have been described by several groups. Thus, Arancibia *et al* ((Int J of Clin Pharm, Ther and Tox, 1987, 25, 97-100) describe the pharmacokinetic properties and bioavailability of a controlled release formulation comprising 500 mg of amoxicillin. No further details

of the formulation are provided. The formulation was however designed to release 21 to 35% during the first 60 minutes, 51 to 66% at 4 hours, 70 to 80% at 6 hours, 81 to 90% at 8 hours and more than 94% at 12 hours. They however found little, if any, correlation between the *in vitro* dissolution rate and the pharmacokinetic behaviour in the body. Hilton *et al* (International Journal of Pharmaceutics, 1992, 86, 79-88) described an alternative controlled release tablet having a hydrophilic polymer matrix and a gas release system, to provide intra-gastric buoyancy, to enhance gastric retention time. This showed no advantage over a conventional capsule formulation, with bioavailability being diminished. In contrast, Hilton *et al* (Journal of Pharmaceutical Sciences, 1993, 82, 737-743) described a 750 mg controlled release tablet incorporating the enteric polymer hydroxypropylmethyl cellulose acetate succinate. This however failed to show any advantage over a conventional capsule. In particular, the bioavailability was reduced to 64.6% compared with the same dosage provided in a capsule. More recently, Hoffman *et al* (Journal of Controlled Release, 1998, 54, 29-37 and WO 98/22091) have described a tablet comprising 500 mg of amoxicillin in a matrix comprising hydroxypropyl methyl cellulose, designed to release 50% of its contents in the first three hours and complete the drug release process over eight hours. The time above MIC was found to be significantly extended, compared to a capsule formulation, but not enough for a 12 h dosing interval. The discussion is in the context of a theoretical MIC of 0.2 µg/ml.

Part of the challenge in providing formulations of amoxicillin in which the drug release is effectively modified (and a ready explanation for the lack of success in the studies already referenced) is the relatively narrow window for absorption of the drug in the small intestine and the relatively short elimination half life of the drug. Furthermore, the rapid elimination of amoxicillin (half-life is about 1.3 hours) makes it difficult to maintain serum levels as clearance from the body is very rapid. Absorption over a prolonged period is therefore required to maintain adequate circulating concentrations of amoxicillin.

In existing tablet formulations comprising amoxicillin and potassium clavulanate, amoxicillin is present in the form amoxicillin trihydrate, as the use of this form provides tablets with greater storage stability than those in which amoxicillin is present as sodium amoxicillin (see GB 2 005 538, Beecham Group Ltd). Sodium amoxicillin is, however, used as the amoxicillin component in existing formulations of amoxicillin and potassium clavulanate adapted for i.v. administration. The form of sodium amoxicillin used is a spray-dried form. In addition, EP 0 131 147-A1 (Beecham Group plc) describes a further form of sodium

amoxicillin, so-called "crystalline sodium amoxicillin". A further process for preparing salts of amoxicillin, including sodium amoxicillin, is described in WO 99/62910 (SmithKline Beecham). Sodium amoxicillin is relatively water soluble in comparison to amoxicillin trihydrate.

5 Formulations comprising clavulanic acid and a pharmaceutically acceptable organic acid or a salt-like derivative thereof, for example calcium citrate, have been described in WO 96/07408 (SmithKline Beecham). In such formulations, it is postulated that the presence of the calcium citrate would help suppress the gastro-intestinal intolerance associated with oral dosing of clavulanate-containing products.

10 Furthermore, US patent no. 5 051 262 (Elan Corp) describes the incorporation of an organic acid into a modified release formulation, to provide a microenvironment in which the locally modified pH helps to protect the active ingredient from degradation.

15 For β -lactams, including amoxicillin, it is recognised that the time above minimum inhibitory concentration (hereinafter "T > MIC") is the pharmacodynamic parameter most closely related to efficacy. For amoxicillin/clavulanate, killing was observed when serum concentrations exceeded the MIC for only 30% of the dosing interval (Craig and Andes, Ped Inf Dis J, 1996, 15, 255-259).

20 A further parameter which may be of importance is the ratio of the maximum plasma concentration (C_{max}) to the MIC value, as this may be related to the potential to select for resistance. Too low a ratio may encourage the development of resistant strains. Preferably, the plasma C_{max} value is well above the MIC value, for instance, at least two times, more preferably at least three times, most preferably at least four times, the MIC value.

25 In a clinical study using the existing Augmentin 875/125 mg tablet, it was found that, when dosed at 12 hour intervals, the T > MIC was about 40% for an MIC of 2 μ g/ml but only about 30% for an MIC of 4 μ g/ml. The existing Augmentin 875/125 mg tablet has a C_{max} value of 11.6 ± 2.8 μ g/ml (Physicians Desk Reference, Medical Economics Co, 52 edition, 1998, 2802).

30 PCT/IB00/00992 describes a new modified release formulation of amoxicillin and clavulanate, comprising for instance, a 1000/62.5 mg bilayer tablet which has an immediate release layer comprising about 563 mg amoxicillin and 62.5 mg clavulanate and a slow release layer comprising about 483 mg of sodium amoxicillin in combination with citric acid and xanthan gum as release modifying excipients. In addition, this application describes a BID dosage regimen using two of these tablets, every 12 hours, for treating bacterial infections, which regimen provides a T>MIC of at least 4.8h, for an MIC of 4 μ g/ml. Such a regimen is

particularly useful for treating penicillin resistant *S. pneumoniae* (PRSP). Penicillin resistance in *S. pneumoniae* can be assessed according to criteria developed by the National Committee for Clinical Laboratory Standards (NCCLS), as follows:

- 5 susceptible strains have MICs of $\leq 0.06 \text{ } \mu\text{g/ml}$, intermediate resistance is defined as
an MIC in the range 0.12 to 1.0 $\mu\text{g/ml}$ whilst penicillin resistance is defined as an
MIC of $\geq 2 \text{ } \mu\text{g/ml}$.

The original dosage regimens developed for amoxicillin/clavulanate combinations were for three times daily (TID) dosing. These were later complemented by regimens having equivalent clinical efficacy but for twice daily
10 dosing (BID), with new formulations for use therein, for instance the 875/125 mg tablet. There still however remains an unmet need to provide new formulations of amoxicillin/clavulanate which offer the convenience of dosing once a day, in particular for use in areas where the incidence of Drug/Penicillin Resistant *S*
15 *pneumoniae* (D/PRSP) is still relatively low, so that it is not necessary to have such a high target MIC for clinical efficacy. Once daily dosing is already possible with some other classes of anti-biotic compounds, notably azithromycin.

Accordingly, in a first aspect, the present invention provides for a pharmaceutical formulation to provide a unit dosage of amoxicillin and potassium clavulanate which comprises from 100 to 150 mg of potassium clavulanate and from
20 1700 to 2500 mg of amoxicillin; which formulation is a modified release formulation comprising an immediate and a slow release phase and in which all of the potassium clavulanate and from 0 to 50% of the amoxicillin is in an immediate release phase and from 50 to 100% of the amoxicillin is in a slow release phase; such that the mean T>MIC is at least 8 h for an MIC of 2 $\mu\text{g/ml}$.

25 Typically, the unit dosage comprises about 125 mg of potassium clavulanate.
Preferably, the unit dosage comprises from 1900 to 2250, typically about
2000 mg of amoxicillin.

30 Preferably, the slow release phase comprises from 60 to 90, more preferably 70 to 90, yet more preferably 76 to 90 % of the total amoxicillin content.

35 Preferably, the mean T>MIC is at least 8.4, 8.8, 9.2, 9.6 h.
Representative unit dosages include 1750/125, 2000/125, and 2250/125 mg of amoxicillin and potassium clavulanate, respectively. A preferred dosage is 2000/125 mg of amoxicillin and potassium clavulanate.

40 The unit dosage of a modified release formulation according to the present invention may conveniently be provided as a number of swallow tablets or capsules, for instance two, three or four, some of which may be the same and some of which may comprise amoxicillin only and no potassium clavulanate. Thus, for instance, a

dosage of 2000 mg amoxicillin and 125 mg potassium clavulanate may be provided by two tablets each comprising 1000/62.5 mg amoxicillin/potassium clavulanate, one tablet comprising 1000 mg of amoxicillin and one tablet comprising 1000/125 mg amoxicillin/potassium clavulanate, two tablets each comprising 500 mg amoxicillin and one tablet comprising 1000/125 mg amoxicillin/potassium clavulanate or four tablets each comprising tablet 500/32.25 mg amoxicillin/potassium clavulanate. In addition, a dosage of 1750 mg amoxicillin and 125 mg potassium clavulanate may be provided by two tablets each comprising 875/62.5 mg amoxicillin/potassium clavulanate or one tablet comprising 875 mg of amoxicillin and one tablet comprising 875/125 mg amoxicillin/potassium clavulanate.

The dosage in a modified release formulation may be provided as a single tablet. Because of the quantities of drug substance being used, this would preferably be other than a swallow tablet, for instance a dispersible tablet or a chewable tablet which may also be effervescent and/or dispersible. The unit dosage may also be conveniently provided as a single dosage sachet or as granules, for direct ingestion, for instance on a spoon or after sprinkling on food. It will be appreciated that the unit dosage may also be provided as a number of smaller non-swallow tablets or sachets, for instance 2 x 1000/62.5 mg or 4 x 500/32.25 mg amoxicillin/potassium clavulanate.

The unit dosage of the present invention is typically provided either as two smaller units each of which provides half the unit dosage or a single formulation which provides the whole of the unit dosage. Accordingly, in a further aspect, the present invention provides a pharmaceutical formulation of amoxicillin and potassium clavulanate which comprises from 50 to 75 mg of potassium clavulanate and from 850 to 1250 mg of amoxicillin or from 100 to 150 mg of potassium clavulanate and from 1700 to 2500 mg of amoxicillin; which formulation is a modified release formulation comprising an immediate and a slow release phase and in which all of the potassium clavulanate and from 0 to 60% of the amoxicillin is in an immediate release phase and from 40 to 100% of the amoxicillin is in a slow release phase; such that the parameter mean $T > MIC$ is at least 8 h for an MIC of 2 $\mu\text{g}/\text{ml}$.

Typically, the formulation comprises about 62.5 mg of potassium clavulanate and from 950 to 1125, typically about 1000 mg of amoxicillin; or about 125 mg of potassium clavulanate and from 1900 to 2250, typically about 2000 mg of amoxicillin.

Preferably, the slow release phase comprises from 60 to 90, more preferably 70 to 90, yet more preferably 76 to 90 % of the total amoxicillin content.

Preferably, T>MIC is at least 8.4, 8.8, 9.2, 9.6 h.

It will be appreciated that the smaller (half) units will typically be a swallow 5 tablet whilst the larger units will typically be a chewable or dispersible tablet or a single dose sachet.

Preferably, the mean plasma concentration of amoxicillin and the mean maximum plasma concentration of amoxicillin are measured after oral administration of a formulation comprising amoxicillin at the start of a meal.

10 The term "amoxicillin" is used generically to refer to amoxicillin or an alkaline salt thereof, in particular amoxicillin trihydrate and (crystallised) sodium amoxicillin, without distinction and unless otherwise indicated.

15 Unless otherwise indicated, weights of amoxicillin and (potassium) clavulanate refer to the equivalent weights of the corresponding free acids. In addition, it will be appreciated that in practice, weights of amoxicillin and clavulanate to be incorporated into a formulation will be further adjusted, in accord with conventional practice, to take account of the potency of the amoxicillin and clavulanate.

20 As used herein, the term "immediate release" refers to the release of the majority of the active material content within a relatively short time, for example within 1 hour, preferably within 30 minutes, after oral ingestion. Examples of such immediate release formulations include conventional swallow tablets, dispersible tablets, chewable tablets, single dose sachets and capsules.

25 As used herein, the term "slow release" refers to the gradual but continuous or sustained release over a relatively extended period of the active material content (in this case amoxicillin) after oral ingestion and which starts when the formulation reaches the stomach and starts to disintegrate/dissolve. The release will continue over a period of time and may continue through until and after the formulation reaches the intestine. This can be contrasted with the term "delayed release" in 30 which release of the active does not start immediately the formulation reaches the stomach but is delayed for a period of time, for instance until when the formulation reaches the intestine when the increasing pH is used to trigger release of the active from the formulation.

35 Preferably, the modified release formulation has a biphasic profile *in vivo* with respect to amoxicillin, that is an initial burst from the immediate release phase to provide an acceptable C_{max} value, supplemented by a further contribution from the slow release phase, to extend the T>MIC parameter to an acceptable value.

Preferably, the modified release formulation provides an "Area Under the (plasma concentration versus time) Curve" (AUC) value which is substantially similar to, for instance at least 80%, preferably at least 90%, more preferably about 100%, of that of the corresponding dosage of amoxicillin taken as a conventional 5 (immediate release) formulation, over the same dosage period, thereby maximising the absorption of the amoxicillin component from the slow release component.

The pharmacokinetic profile for a dosage of the present invention may be readily determined from a single dosage bioavailability study in human volunteers. Plasma concentrations of amoxicillin may then be readily determined in blood 10 samples taken from patients according to procedures well known and documented in the art.

Preferably, the modified release formulations of the present invention are formulated such that the release of amoxicillin is effected predominantly through the stomach and small intestine, so that absorption through the specific amoxicillin 15 absorption site in the small intestine is maximised. Preferably, the amoxicillin release profile is made up of a contribution from an immediate release component which is then complemented and extended by an on-going contribution from a slow release component. Preferably, potassium clavulanate is released substantially immediately from the formulation, when the formulation reaches the stomach and is 20 absorption begins immediately, thereby minimising the risk of degradation from prolonged exposure to the stomach. Such formulations are preferably formulated such that the release of amoxicillin and potassium clavulanate occurs predominantly within 3 hours of ingestion of the formulation.

Preferably, the modified release formulation is a tablet. Representative 25 modified release tablets comprise about 62.5 mg of potassium clavulanate in the immediate release phase, from 0 to 500 mg amoxicillin in the immediate release phase and from 500 to 1000 mg amoxicillin in the slow release phase, for instance:

(a) a tablet comprising 1000 mg amoxicillin and 62.5 mg potassium 30 clavulanate, in which the immediate release phase comprises 62.5 mg $\pm 5\%$ of potassium clavulanate and 250 mg $\pm 5\%$ amoxicillin and the slow release phase comprises 750 mg $\pm 5\%$ of amoxicillin; or

(b) a tablet comprising 875 mg amoxicillin and 62.5 mg potassium 35 clavulanate, in which the immediate release phase comprises 62.5 mg $\pm 5\%$ of potassium clavulanate and 275 mg $\pm 5\%$ amoxicillin, and the slow release phase about 600 mg of amoxicillin.

It will be appreciated that when the unit dose is provided as a single unit, for instance a chewable tablet or a single dose sachet, such unit will comprise twice the above quantities.

For a tablet formulation, the immediate and slow release phases may be
5 provided in a number of different formats.

In a preferred aspect, the immediate and slow release phases are provided as separate layers of a layered tablet.

Accordingly, in a further aspect, the present invention provides for a layered tablet formulation comprising potassium clavulanate and amoxicillin in an
10 immediate release layer phase and amoxicillin in a slow release layer. The layered tablet may have two layers, or two layers plus one or more barrier layer, as well as a coating layer. As used herein, the term "bilayer" tablet refers to a tablet consisting of an immediate release and a slow release layer, optionally with a coating layer.

An immediate release layer may be, for example, a layer which disintegrates
15 immediately or rapidly and has a composition similar to that of known tablets which disintegrate immediately or rapidly. For example, the layer may comprise, in addition to the active material content, excipients including diluents such as microcrystalline cellulose; disintegrants such as cross-linked polyvinylpyrrolidone (CLPVP), sodium starch glycollate; compression aids such as colloidal silicon
20 dioxide and microcrystalline cellulose; and lubricants such as magnesium stearate. Such an immediate release layer may comprise around 60 to 85 % (all percentages given herein are on a weight percentage basis unless otherwise stated), preferably 70 to 85 %, of active material content, around 10 to 30 %, preferably 10 to 20 % of fillers/compression aids, and conventional amounts of disintegrants and lubricants,
25 typically about 0.5 to 3%, etc.

An alternative type of immediate release layer may be a swellable layer having a composition which incorporates polymeric materials which swell immediately and extensively in contact with water or aqueous media, to form a water permeable but relatively large swollen mass. Active material content may be
30 immediately leached out of this mass.

Slow release layers have a composition which comprises amoxicillin together with a release retarding excipient which allows for slow release of amoxicillin. Suitable release retarding excipients include pH sensitive polymers, for instance polymers based upon methacrylic acid copolymers such as the Eudragit (trade mark)
35 polymers, for example Eudragit L (trade mark) which may be used either alone or with a plasticiser; release-retarding polymers which have a high degree of swelling in contact with water or aqueous media such as the stomach contents; polymeric

materials which form a gel on contact with water or aqueous media; and polymeric materials which have both swelling and gelling characteristics in contact with water or aqueous media.

Release retarding polymers which have a high degree of swelling include,
5 *inter alia*, cross-linked sodium carboxymethylcellulose, cross-linked hydroxypropylcellulose, high-molecular weight hydroxypropylmethylcellulose, carboxymethylamide, potassium methacrylatedivinylbenzene co-polymer, polymethylmethacrylate, cross-linked polyvinylpyrrolidone, high-molecular weight polyvinylalcohols etc.

10 Release retarding gellable polymers include methylcellulose, carboxymethylcellulose, low-molecular weight hydroxypropylmethylcellulose, low-molecular weight polyvinylalcohols, polyoxyethyleneglycols, non-cross linked polyvinylpyrrolidone, xanthan gum etc.

15 Release retarding polymers simultaneously possessing swelling and gelling properties include medium-viscosity hydroxypropylmethylcellulose and medium-viscosity polyvinylalcohols.

A preferred release-retarding polymer is xanthan gum, in particular a fine mesh grade of xanthan gum, preferably pharmaceutical grade xanthan gum, 200 mesh, for instance the product Xantural 75 (also known as Keltrol CR, Trade Mark,
20 Monsanto, 800 N Lindbergh Blvd, St Louis, MO 63167, USA). Xanthan gum is a polysaccharide which upon hydration forms a viscous gel layer around the tablet through which the active has to diffuse. It has been shown that the smaller the particle size, the slower the release rate. In addition, the rate of release of drug substance is dependent upon the amount of xanthan gum used and can be adjusted to give the desired profile. Controlled release formulations comprising from 7.5 to
25% xanthan gum are described in EP 0 234 670-A (Boots Co plc). The preferred embodiment is a tablet comprising ibuprofen as the drug substance and 15-20% xanthan gum, which is taken once daily.

Examples of other polymers which may be used include Methocel K4M
30 (Trade Mark), Methocel E5 (Trade Mark), Methocel E5O (Trade Mark), Methocel E4M (Trade Mark), Methocel K15M (Trade Mark) and Methocel K100M (Trade Mark). An example of a suitable polymer mixture is a mixture of Methocel E5 and K4M, for example 1:1, w:w.

Other known release-retarding polymers which may be incorporated include
35 hydrocolloids such as natural or synthetic gums, cellulose derivatives other than those listed above, carbohydrate-based substances such as acacia, gum tragacanth, locust bean gum, guar gum, agar, pectin, carageenin, soluble and insoluble alginates,

carboxypolyethylene, casein, zein, and the like, and proteinaceous substances such as gelatin.

Such a slow release layer may contain polymers which immediately swell in contact with water or aqueous media so that they form a relatively large swollen mass which is not immediately discharged from the stomach into the intestine.

The slow release layer may also include diluents such as lactose; compression aids such as microcrystalline cellulose; and lubricants such as magnesium stearate. The slow release layer may further comprise disintegrants, such as cross-linked polyvinylpyrrolidone (CLPVP) and sodium starch glycollate; binders such as povidone (polyvinylpyrrolidone); desiccants, such as silicon dioxide; and soluble excipients such as mannitol or other soluble sugars. Typically, the slow release layer comprises from about 60 to 80% by weight of amoxicillin; from 10 to 20 % by weight of diluent/compression aid and from 1 to 2.5 % by weight of lubricant.

When xanthan gum is used as release-retarding polymer, the layer contains from 60 to 80% of amoxicillin, from 4 to 25%, preferably 4 to 15%, more preferably 5 to 15%, typically about 6 to 10%, of xanthan gum, from 10 to 30%, preferably 10 to 20% of fillers/compression aids, and conventional quantities of lubricants, all % being by weight of the layer. In a preferred embodiment, the slow release layer comprises from 70 to 80% of amoxicillin, from 5 to 10%, of xanthan gum, from 10 to 20% of microcrystalline cellulose, and from 1 to 2.5 % of magnesium stearate, all % being by weight of the layer.

When release-retarding polymers other than xanthan gum are used, the slow release layer may contain around 30 to 70%, preferably from 40 to 60%, of amoxicillin, from 15 to 45% of release-retarding polymer, from 0 to 30% of fillers/compression aids, conventional quantities of lubricants, and from 5 to 20% of soluble excipients, all % being by weight of the layer.

A further release retarding excipient for use when the amoxicillin in the slow release layer is in the form of a soluble salt thereof, such as sodium or potassium amoxicillin, is an organic acid.

Preferably, the organic acid is a pharmaceutically acceptable organic acid present in a molar ratio of from 100:1 to 1:10, preferably 50:1 to 1:5, more preferably 20:1 to 1:2 (amoxicillin to organic acid).

It is believed that intimate contact between the organic acid and the salt of amoxicillin in the pharmaceutical formulation, for instance as a consequence of compacted granule formation or direct compression in a tablet, causes some form of

interaction which modifies the release of the amoxicillin component from the formulation.

Soluble pharmaceutically acceptable salts of amoxicillin include alkali metal salts such as sodium and potassium; alkaline earth metal salts such as magnesium and calcium, and acid salts such as amoxicillin hydrochloride. Preferably, the salt is sodium amoxicillin, more preferably crystallised sodium amoxicillin.

As used herein, the term "pharmaceutically acceptable organic acid" refers to organic acids which are without pharmacological effect *per se*, have acceptable organo-leptic properties, have acceptable density, do not have an extreme pH and are preferably solid. Examples thereof include mono-carboxylic acids and poly-carboxylic acids having from 2 to 25, preferably from 2 to 10, carbon atoms; monocyclic and polycyclic aryl acids such as benzoic acid; as well as monohydrogen, dihydrogen etc metal salts of multi-valent acids. A single pharmaceutically acceptable organic acid may be used, or two or more of such may be used in combination. Preferably, the organic acid is a C(2-10)alkyl- or alkenyl-carboxylic acid having from one, two or three carboxylic acid groups, and optionally with one or more hydroxy substituents or an additional CO group in the carbon chain, for instance malonic acid, succinic acid, fumaric acid, maleic acid, adipic acid, lactic acid, levulinic acid, sorbic acid or a fruit acid such as tartaric acid, malic acid, ascorbic acid or citric acid, or an acidic salt thereof; more preferably citric acid, in particular anhydrous citric acid.

The organic acid may be used alone or in combination with a release retarding polymer as hereinbefore described. A preferred combination comprises citric acid and a release retarding gellable polymer, in particular xanthan gum. In the presence of the organic acid, for instance citric acid, xanthan gum may be used at a lower level than when included on its own, for instance, from 0.5 to 8%, preferably 1 to 5%, typically about 2%, by weight of the slow release layer.

When an organic acid is used as a release-retarding excipient, the slow release layer contains from 60 to 80% of a soluble salt of amoxicillin, from 10 to 30%, preferably 10 to 20% of fillers/compression aids, and conventional quantities of lubricants, all % being by weight of the layer. In a preferred embodiment, the slow release layer comprises from 60 to 70 % of a soluble salt of amoxicillin, from 10 to 20% of microcrystalline cellulose, and from 1 to 2.5 % of magnesium stearate, all % being by weight of the layer.

In a representative example, a layered tablet comprises in the slow release layer crystallised sodium amoxicillin and citric acid, in a molar ratio of about 50:1 to 1:2, preferably 20:1 to 1:2, more preferably 2:1 to 1:1.2, yet more preferably about

1:1. In a representative embodiment, the slow release layer comprises 750 mg $\pm 5\%$ crystallised sodium amoxicillin, and about 134 mg $\pm 10\%$ citric acid.

In a representative layered tablet comprising 1000 mg amoxicillin and 62.5 mg potassium clavulanate, the immediate release layer comprises 250 mg $\pm 5\%$ amoxicillin, preferably amoxicillin trihydrate, and about 62.5 mg $\pm 5\%$ of potassium clavulanate and the slow release layer 750 mg $\pm 5\%$ of amoxicillin, preferably crystallised sodium amoxicillin, and 134 mg $\pm 10\%$ citric acid.

The tablet formulations of the invention may also include one or more barrier layers, which may be located between the respective first and second layers, and/or on one or more of the outer surfaces of the first and second layers, for example the end faces of the layers of a substantially cylindrical tablet. Such barrier layers may, for example, be composed of polymers which are either substantially or completely impermeable to water or aqueous media, or are slowly erodable in water or aqueous media or biological liquids and/or which swell in contact with water or aqueous media. Suitably the barrier layer should be such that it retains these characteristics at least until complete or substantially complete transfer of the active material content to the surrounding medium.

Suitable polymers for the barrier layer include acrylates, methacrylates, copolymers of acrylic acid, celluloses and derivatives thereof such as ethylcelluloses, cellulose acetate propionate, polyethylenes and polyvinyl alcohols etc. Barrier layers comprising polymers which swell in contact with water or aqueous media may swell to such an extent that the swollen layer forms a relatively large swollen mass, the size of which delays its immediate discharge from the stomach into the intestine. The barrier layer may itself contain active material content, for example the barrier layer may be a slow or delayed release layer. Barrier layers may typically have an individual thickness of 2 mm to 10 microns.

Suitable polymers for barrier layers which are relatively impermeable to water include the Methocel (trade mark) series of polymers mentioned above, for example Methocel K100M, Methocel K15M, Methocel E5 and Methocel E50, used singly or combined, or optionally combined with an Ethocel (trade mark) polymer. Such polymers may suitably be used in combination with a plasticiser such as hydrogenated castor oil. The barrier layer may also include conventional binders, fillers, lubricants and compression acids etc such as Polyvidon K30 (trade mark), magnesium stearate, and silicon dioxide, e.g. Syloid 244 (trade mark).

The tablet formulation of the invention may be wholly or partly covered by a coating layer, which may be a protective layer to prevent ingress of moisture or damage to the tablet. The coating layer may itself contain active material content,

and may, for example, be an immediate release layer, which immediately disintegrates in contact with water or aqueous media to release its active material content, for example amoxicillin and potassium clavulanate. Preferred coating materials comprise hydroxypropylmethylcellulose and polyethylene glycol, with 5 titanium dioxide as an opacifying agent, for instance as described in WO 95/28927 (SmithKline Beecham).

As well as active material content etc, the tablet of the invention may also include a pH modifying agent, such as a pH buffer, which may be contained in either the immediate-, or slow-release layers, or in a coating around all or part of the tablet.

10 A suitable buffer is calcium hydrogen phosphate.

In a tablet without a barrier layer, the immediate release layer comprises from 50 to 60% and the slow release layer comprises from 40 to 50% of the overall tablet weight. When a barrier layer is present, the immediate release layer typically comprises from 40 to 50%, the slow release layer comprises from 35 to 45%, and the 15 barrier layer comprises from 5 to 20% of the overall tablet weight.

It is found that a satisfactory pharmacokinetic profile may be obtained from a bilayered tablet of the present invention without the need to include a barrier layer. Accordingly, a bi-layer tablet is preferred. This also reduces the complexity of the manufacturing process.

20 It will be appreciated that layered tablets having an immediate release layer and a slow release layer as hereinbefore described are novel. Accordingly, in a further aspect, the present invention provides for a pharmaceutical layered tablet formulation comprising an immediate release layer and a slow release layer and comprising from 700 to 1250 mg, typically 1000 mg, amoxicillin, and from 50 to 75 mg, typically 62.5 mg, potassium clavulanate, such that all the potassium clavulanate and from 0 to 60% of the amoxicillin is in the immediate release layer and from 40 25 to 100% of the amoxicillin is in the immediate release layer, in combination with pharmaceutically acceptable excipients or carriers. Preferably, the layered tablet is a bi-layered tablet.

30 Suitably the tablet formulations of the invention may be formed by known compression tableting techniques, for example using a known multi-layer tableting press. Preferably, in a preliminary step, slugging or roller compaction is used to form granulates. Lubricants and compression aids (if used) are then added, to form a compression blend for subsequent compaction.

35 Representative bilayer tablets of the present invention may be made by a process which comprises, as an early phase, the formation of slow release compacted granules, comprising the steps of milling sodium amoxicillin, a portion of the diluent

/ compression aid such as microcrystalline cellulose (typically about 30%), a portion of the lubricant (typically about 70%) and a pharmaceutically acceptable organic acid such as a fruit acid, for instance citric acid, and then blending with a release retarding polymer such as xanthan gum, if present, and a compression aid such as

5 colloidal silicon dioxide, compacting the blend, for instance in a roller compactor or by slugging, and then milling, to form slow release granules. Preferably such granules have a size in the range 100 to 1000 microns. The incorporation of xanthan gum appears to also have an unexpected benefit on processability.

Alternatively, slow release granules in which amoxicillin is present as
10 amoxicillin trihydrate and the release modifying excipient is xanthan gum may be prepared by a similar process

Such slow release compacted granules may then be blended with other excipients such as the remaining magnesium stearate and microcrystalline cellulose, to form a slow release compression blend.

15 In addition, amoxicillin trihydrate, potassium clavulanate (preferably as 1:1 blend with microcrystalline cellulose), microcrystalline cellulose (a portion of total used), are milled and blended with a lubricant such as magnesium stearate (preferably about 50% of the total), and then compacted, for instance in a roller compactor or by slugging, and milled to form immediate release compacted
20 granules. These immediate release compacted granules may then be blended with other excipients such as the remaining magnesium stearate and microcrystalline cellulose (about 13%), a compression aid such as colloidal silica, and a disintegrant such as sodium starch glycollate, to form an immediate release compression blend.

The immediate release and slow release compression blends may then be
25 compressed as separate layers on a bilayer tablet press, to form bilayer tablets.

Such slow release granules are novel. Accordingly, in a further aspect, the present invention provides for compacted granules comprising a soluble salt of amoxicillin, for instance sodium amoxicillin, a diluent/compression aid, and an organic acid or a release retarding polymer or a mixture thereof, as hereinbefore defined. In a yet further aspect, the present invention also provides for compacted
30 granules comprising amoxicillin, for instance amoxicillin trihydrate or sodium amoxicillin, a diluent/compression aid, and a release retarding polymer, for instance xanthan gum, as hereinbefore defined.

Alternatively, a dry densification process may be used, e.g. briquetting.
35 Typically the active material content, pH modifiers, buffers, fillers and/or diluent, release retarding agents, disintegrants and binders, when used are mixed, then lubricants and compression aids are added. The complete mixture may then be

compressed under high pressure in the tablet press. A wet granulation process may be also be used, for instance with isopropanol as the solvent and Polyvidon K-30 (trade mark) as the wet granulating aid.

A barrier layer, if present, may typically be made up by a wet granulation
5 technique, or by dry granulation techniques such as roller compaction. Typically the barrier material, e.g. Methocel (trade mark) is suspended in a solvent such as ethanol containing a granulation acid such as Ethocel or Polyvidon K-30 (trade mark), followed by mixing, sieving and granulation. Typically a first layer may be formed, then a barrier layer deposited upon it, e.g. by compression, spraying or immersion
10 techniques, then the second layer may be formed so that the barrier layer is sandwiched between the first and second layers. Additionally, or alternatively, the first and second layers may be formed and a barrier layer may then be formed, for instance by compression, spraying or immersion, on one or more of the end faces of the tablet.

15 A process for the preparation of crystallised sodium amoxicillin is described in EP-A-0 131 147 (Beecham Group plc).

Potassium clavulanate is known to be extremely water sensitive. Therefore tablet formulations which contain potassium clavulanate should be made up in dry conditions, preferably at 30% relative humidity or less, and the ingredients of the
20 formulation should be pre-dried where appropriate. Tablet formulations of the invention should be stored in containers which are sealed against the ingress of atmospheric moisture.

Tablet cores may then be coated with a coating layer which may be applied from an aqueous or an organic solvent system, preferably an aqueous solvent system,
25 to provide film coated tablets.

The invention also provides a method for the manufacture of a tablet formulation as described above comprising the steps of forming said first and second layers, and any barrier layers and coating layer(s) which may be present.

In addition to the layered tablet approach hereinbefore described, other types
30 of tablet may be used to provide an immediate release phase and a slow release phase, using the excipients hereinbefore described but providing the phases in different formats. Thus, the slow release phase may form the core of a tablet which is then surrounded by an outer casing forming the immediate release phase, optionally with an intermediate coating layer around the core and/or a final coating
35 layer around the outer casing (see WO 95/28148, SmithKline Beecham). The slow release phase may also be provided as granules which are dispersed in a matrix of

amoxicillin and potassium clavulanate, the matrix forming the immediate release phase (see WO 96/04908, SmithKline Beecham).

In a further variant, a monolith modified release tablet may be prepared from slow release compacted granules comprising amoxicillin, a diluent/compression aid such as microcrystalline cellulose, and a pharmaceutically acceptable organic acid such as a fruit acid, for instance citric acid (if amoxicillin is present as a soluble salt thereof), or a release retarding polymer such as xanthan gum or a mixture thereof, preferably a release retarding polymer (as hereinbefore described); and immediate release compacted granules comprising amoxicillin and potassium clavulanate (as hereinbefore described) or immediate release compacted granules comprising amoxicillin and potassium clavulanate, for instance in a 2:1 ratio, and further immediate release compacted granules comprising amoxicillin (as described in WO 98/35672, SmithKline Beecham Laboratoires Pharmaceutiques), the granules being combined with extragranular excipients to form tablets. Such granules may also be processed into other pharmaceutical formulations, for instance single dosage sachets, capsules or chewable tablets comprising a unit dosage as hereinbefore described.

Chewable tablets according to the present invention typically comprise a chewable base formed from, for instance, mannitol, sorbitol, dextrose, fructose or lactose alone or in combination. A chewable tablet may also comprise further excipients, for instance, disintegrants, lubricants, sweetening agents, colouring and flavouring agents. Such further excipients together will preferably comprise from 3 to 10%, more preferably 4 to 8%, yet more preferably 4 to 7% by weight of the tablet. Disintegrants may be present in from 1 to 4%, preferably from 1 to 3%, more preferably from 1 to 2% by weight of the tablet. Representative disintegrants include crospovidone, sodium starch glycollate, starches such as maize starch and rice strach, croscarmellose sodium and cellulose products such as microcrystalline cellulose, microfine cellulose, low substituted hydroxy propyl cellulose, either used singly or in admixture. Preferably, the disintegrant is crospovidone. Lubricants may be present in from 0.25 to 2.0%, preferably from 0.5 to 1.2% by weight of the tablet. Preferred lubricants include magnesium stearate. Preferably, the sweetening agent is an artificial sweetening agent such as sodium saccharin or aspartame, preferably aspartame, which may be present in from 0.5 to 1.5% by weight of the tablet. Preferably, a tablet of the present invention is substantially free of sugar (sucrose). Preferred flavouring agents include fruit flavours which may be natural or synthetic, for instance peppermint, cherry and banana, or a mixture thereof.

Single dose sachets according to the present invention comprise, in addition to the drug substance, excipients typically included in a sachet formulation, such as a

sweetener, for instance aspartame, flavourings, for instance fruit flavours, optionally a suspending agent such as xanthan gum, as well as silica gel, to act as a desiccant.

Capsules according to the present invention comprise, in addition to the drug substance, excipients typically included in a capsule, for instance starch, lactose,

5 microcrystalline cellulose, magnesium stearate. It will be appreciated that due to the hygroscopic nature of clavulanate, the use of materials such as gelatin for forming the capsules should be avoided. Preferably, capsules are prepared from materials such as HPMC or a gelatin/PEG combination.

In a further embodiment, the slow release phase may be provided as a
10 separate component, for instance as a separate tablet, so that the unit dosage is provided as a combination of a conventional component in which amoxicillin and potassium clavulanate are released immediately, optionally with a conventional amoxicillin formulation such as a tablet, and a further formulation, for instance a tablet, comprising amoxicillin (and no potassium clavulanate) from which
15 amoxicillin is released slowly. The weight of potassium clavulanate and the combined weights of amoxicillin in the conventional and slow release formulations will provide the overall unit dosage. Thus, for instance a dosage of 2000/125 mg may be provided by a combination of an existing 250/125 mg amoxicillin/potassium clavulanate tablet and in combination with 2 slow release tablet comprising 875 mg
20 of amoxicillin, respectively. Furthermore, a dosage of 1750/125 mg may be provided by an existing 875/125 mg tablet (as described in WO 95/28927, SmithKline Beecham) in combination with a slow release tablet comprising 875 mg of amoxicillin.. Accordingly, in a further aspect, the present invention provides for a
25 kit comprising a conventional (immediate release) tablet comprising amoxicillin and potassium clavulanate, optionally with a conventional (immediate release) tablet comprising amoxicillin, and a slow release tablet comprising amoxicillin (and no potassium clavulanate).

Representative slow release amoxicillin tablets are described in
PCT/IB00/00992.

30 Preferably, the unit dosage forms of the present invention are packaged in containers that inhibit the ingress of atmospheric moisture, for instance blister packs, tightly closed bottles or desiccated pouch packs etc which are conventional in the art. Preferably, bottles also include a desiccating material, to preserve the clavulanate. Preferred bottles include HDPE bottles. Preferred blister packs include cold-formed
35 blister packs in which each blister may contain one tablet, or two tablets, where the unit dosage is two tablets, for instance 2 x 1000/62.5 mg tablets, to improve patient compliance. Formulations of the present invention are of use in treating bacterial

infections. Accordingly, in a further aspect, the present invention provides for a method of treating a bacterial infection in a patient in need thereof which method comprises administering an effective amount of a formulation as hereinbefore defined, to a patient in need thereof, once daily, preferably about every 24 h.

5 Infections amenable to treatment by the present method include those caused by the commonly occurring β -lactamase producing respiratory pathogens, most notably *H influenzae* and *M catarrhalis*, such as respiratory tract infections, including community acquired pneumoniae (CAP), acute exacerbations of chronic bronchitis (AECB) and acute bacterial sinusitis (ABS). In addition, the present
10 invention will be useful for treating infections caused by *S pneumoniae* (including *S pneumoniae* having intermediate resistance. Most outpatient respiratory infections are caused by either *S pneumoniae* and/or the β -lactamase producing bacteria and are treated empirically so there is a continuing need for a method of treatment, such as the present invention, that provides a spectrum of activity that covers all such
15 pathogens. The duration of therapy will generally between 7 and 14 days, typically 7 days for indications such as acute exacerbations of chronic bronchitis but 10 days for acute bacterial sinusitis. Typically, the dosages regimens are designed for adult patients, rather than paediatric patients.

20 It will be appreciated that the methods and formulations hereinbefore described for amoxicillin and clavulanate are also applicable to amoxicillin alone, with no clavulanate, particularly for treating infections where β -lactamase producing pathogens are not implicated, for instance infections caused by the organism *Streptococcus pyogenes*, such acute bacterial tonsillitis and/or pharyngitis. The present invention also all such uses and formulations of amoxicillin as the sole agent.
25

The invention will now be described by way of example only with reference to the accompanying drawings, in which:

Fig. 1 shows the structure of various types of layered tablets of the present
30 invention, in particular the structure of substantially cylindrical compressed tablets are shown in longitudinal section. In Fig 1A, the tablet comprises a first layer (1) and a second layer (2), without any barrier layer or coating layer. In Fig 1B, the tablet comprises a first layer (1), a second layer (2), and a barrier layer (3) sandwiched between the first and second layers (1) and (2). In Fig 1C, the tablet
35 comprises a first layer (1), a second layer (2), and a barrier layer (3) located on the end face of the second layer (2). In Fig 1D, the tablet comprises a first layer (1), a second layer (2), a barrier layer (3) sandwiched between the first and second layers

(1) and (2), and a coating layer (4) which partly covers the tablet. The dotted line shows the possibility of the coating layer (4A) covering the entire tablet. In Fig. 1E, the tablet comprises a first layer (1) a second layer (2), and a third layer (3) intermediate between the first and second layers (1) and (2). All three of these layers 5 (1), (2) and (3) include active material content.

All publications and references, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference in their entirety as if each individual publication or reference were specifically and 10 individually indicated to be incorporated by reference herein as being fully set forth. Any patent application to which this application claims priority is also incorporated by reference herein in its entirety in the manner described above for publications and references.

15

Example 1 – 1000 mg monolith tablet

	mg/tablet	%
Crystallised Sodium Amoxicillin ¹	824.2	51.51
Amoxicillin Trihydrate ²	290.7	18.17
Clavulanate Potassium ³	76.2	4.76
Dried Microcrystalline Cellulose	165.9	10.37
Magnesium Stearate	23.0	1.44
Sodium Starch glycollate	80.0	5.00
Colloidal silicon dioxide	6.3	0.39
Citric acid	133.7	8.36
Total	1600	100.0

1 adjusted for potency of the amoxicillin component and corresponding to 750 mg
20 of amoxicillin
2 adjusted for potency of the amoxicillin component and corresponding to 250 mg
of amoxicillin
3 adjusted for potency of the clavulanate potassium component and corresponding
to 62.5 mg of clavulanate potassium

25

Two separate batches of granules, the first, immediate release granules, comprising amoxicillin and potassium clavulanate and the second, slow release granules, comprising sodium amoxicillin and citric acid, were prepared by roller compaction

and then combined with the remaining excipients, blended and formed into tablets in a tablet press.

In further detail, immediate release granules were prepared thus: containers
5 were charged with dried microcrystalline cellulose (1), amoxicillin trihydrate (2) and (5) (in 1:1 ratio), a potassium clavulanate/ dried microcrystalline cellulose blend (1:1) and magnesium stearate (about 50% of total) (4). The contents of containers (1) and (2) were passed through a mesh, milled in a "Fitzmill" operating at 1500 rpm and blended with the contents of container (3). The contents of container (4) were
10 then screened and milled and blended with the initial blend and then blended with the contents of container (5) which had gone through a preliminary screening and milling step. This blend was then subjected to roller compaction using a Chilsonator operating at a pressure of 1000 psi ± 200psi and the product milled and screened through a vibratory screen with 14 and 80 meshes, to provide immediate release
15 granules.

Slow release granules were prepared thus: containers were charged with dried microcrystalline cellulose (about 70%) and anhydrous citric acid (1), sodium amoxicillin (2) and (4) (in a 1:1 ratio), and magnesium stearate (about 70%), colloidal silicon dioxide and xanthan gum (3). The contents of containers (1) and
20 (2) were screened and milled in a Fitzmill, and then blended with the contents of container (3), blended and then the contents of container (4) which had been milled and screened in a preliminary step. This blend was subjected to roller compaction on a chilsonator, operating at a pressure of 600 psi ± 100 psi, milled and screened, to provide slow release granules.

25 The immediate release and slow release granules were blended with the remaining excipients (magnesium stearate, dried microcrystalline cellulose) and then compressed into a monolith tablet on a standard tabletting machine.

Finally, the tablet cores were coated with an aqueous film coating in a 60 inch coating pan, operating on a 300 kg sub-batch. The pan was equipped with 4
30 spray guns and rotated at 3 to 5 rpm. The inlet air was dehumidified with the temperature in the range 56 to 60°C whilst the exhaust air humidity was in the range 4 to 12% and the temperature in the range 43 to 50°C. The spray rate was 80 to 120 ml/min/spray gun.

35 ***in vivo Pharmacokinetic evaluation of formulations***

The bioavailability of a dosage according to the present invention may be evaluated in a human volunteer study, typically an open, randomised, crossover studies in healthy volunteers, for instance using the study design described in PCT/IB00/00992.

5

In a study involving prototype formulations to provide a unit dosage of 2000 mg amoxicillin and 125 mg potassium clavulanate, a dosage made up of a two monolith tablets according to Example 1, was found to have mean T>MIC of about 8.1 h for an MIC = 2 µg/ml (n = 11).

10

The present invention also extends to formulations which are bioequivalent to the tablets the present invention, in terms of both rate and extent of absorption, for instance as defined by the US Food and Drug Administration and discussed in the 15 so-called "Orange Book" (Approved Drug Products with Therapeutic Equivalence Evaluations, US Dept of Health and Human Services, 19th edn, 1999).

Reference Data

- 20 The existing Augmentin 875/125 mg tablet has a mean C_{max} value of 11.6±2.8 µg/ml (Physicians Desk Reference, Medical Economics Co, 52 edition, 1998, 2802). The time above MIC was about 40% of the 12 hour dosing interval for an MIC of 2 µg/ml and about 30% for an MIC of 4 µg/ml (SmithKline Beecham data). The existing Augmentin 500/125 mg tablet has a mean C_{max} value of 6.5±1.4 µg/ml
25 (Physicians Desk Reference, Medical Economics Co, 52 edition, 1998, 2802).